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How FDA Works to Ensure Vaccine Safety

by Isadora B. Stehlin

The gasping for breath and desperate hacking of whooping cough. The iron lungs and braces of polio. Birth defects from rubella. For many people today, those signs of terrible diseases are the stuff of history books, thanks to vaccines. But the rare case of vaccine-associated polio or the death of an infant soon after receiving a dose of pertussis vaccine may make people wonder--are vaccines safe enough, or could they be safer?

For the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER), vaccine safety, along with effectiveness, is central to regulation of these preparations.

Clinical Trials

The first step to licensing a new vaccine is safety testing in animals. If the laboratory animals immunized with the vaccine don't have serious reactions, FDA consults with the vaccine manufacturer or sponsor on further refining of the manufacturing process.

Because the weakened viruses used for vaccines are grown in animal or human cells, "we spend a tremendous amount of time studying the safety of those cells," says M. Carolyn Hardegree, M.D., director of CBER'S office of vaccine research and review.

For example, the manufacturer of the recently licensed Varicella (chickenpox) vaccine had to prove the human cell line used to grow the virus was not contaminated with any other viruses, such as hepatitis.

Only after those studies have been done does testing in people begin.

FDA requires new vaccines to undergo several phases of clinical trials--testing in people--for safety and effectiveness.

Phase 1 trials evaluate basic safety and identify only very serious or very common

adverse events. These trials are small--between 20 and 100 patients--and last just several months.

Phase 2 trials include several hundred patients and last anywhere from several months to two years. This allows for more information on safety and preliminary information on effectiveness to be collected.

Unless severe reactions or a lack of effectiveness surfaces during the first two phases, the trials are expanded in Phase 3 to include several hundred to several thousand people. These trials continue to measure effectiveness and safety.

If, towards or at the end of the Phase 3 trials, the manufacturer believes there are adequate data to show that the vaccine is safe and effective for its intended use, the manufacturer applies to FDA for two licenses--one for the vaccine (product license) and one for the manufacturing plant (establishment license).

An internal FDA committee then reviews the clinical data, proposed labeling, and manufacturing protocols that ensure a consistent product, and the results of the agency's own confirmatory tests of the vaccine's components and the final product. The review process includes an inspection of the manufacturing facility.

Advisory Committees

FDA advisory committees are groups of experts outside government that review data and issues associated with products and recommend what action the agency should take.

"Advisory committees may be brought in at any stage in the review process," says Hardegree. "For example, before we went into Phase 1 trials of some of the first AIDS vaccines, we showed the [proposed studies] to the Vaccines and Related Biological Products Advisory Committee. As we move into determining what might be appropriate efficacy studies, we might let them see that early on." Involving the committees throughout the process is a good idea, she says, because these expert advisors bring a wealth of scientific background to address vaccine issues confronting FDA.

"Through the years, we've been very fortunate to have an outstanding advisory group," says Hardegree. "We've had members who have been willing to serve as consultants for many years after their four-year term, and they provide a continuity on some of the issues that were discussed years ago and are still being studied today."

Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding whether to license a vaccine for marketing.

Green Light

Licensing of a vaccine is only the beginning of FDA's oversight. Manufacturers must

submit samples of each vaccine lot and results of their own tests for potency, safety and purity to the agency before release.

Each lot must be tested because vaccines are derived from living organisms that are sensitive to environmental factors and are susceptible to contamination.

"Tests generally applicable to all products include those for bacterial and fungal sterility, general safety, purity, identity, suitability of constituent materials, and potency," explains Hardegree. "Sterility testing is performed on both bulk- and final-container material. In addition, cell-culture-derived vaccines must be tested for [disease-causing organisms]. All ingredients such as diluents, preservatives or adjuvants must meet generally accepted standards of purity."

The importance of these tests was established years ago. In 1955, the virus-inactivated Salk polio vaccine first went on the market. Unfortunately, virus in some batches of the vaccine produced by one manufacturer was not totally inactivated, and some of the children who got that vaccine developed polio. (See "Assessing Risks with Polio Vaccines".)

Inadequate tests were the culprit, explains Hardegree.

The tests manufacturers must perform on each lot are spelled out in the Code of Federal Regulations or in the product license application. When the manufacturer sends the lot samples, along with the results of testing, to FDA, "we either test the lot sample ourselves or go with the manufacturer's documentation," says Jerome A. Donlon, M.D., Ph.D., director of CBER's office of establishment licensing and product surveillance. With vaccines for diseases that attack the nervous system, such as the live polio vaccine, "we test every lot because of the tremendous potential for harm," he explains.

Over the last 10 years, there have been only three vaccine recalls. One lot was recalled after FDA detected particulates; another was mislabeled. The third lot was recalled because of potential problems after an FDA inspection found violations of good manufacturing practices at the production plant.

Continuing Studies

Although clinical trials are carefully designed to uncover potential adverse reactions before FDA licenses a vaccine, "we obviously can't get all the information premarketing," says Susan Ellenberg, Ph.D., director of CBER's division of biostatistics and epidemiology. "You're never going to be able to do studies big enough to detect risks that might happen at a level of one in 100,000 or one in 1 million. We'd never get vaccines on the market. Still, such risks are important to detect because of the large population exposed. So we have to develop postmarketing surveillance programs."

For some vaccines, there are formal Phase 4 studies under way. At FDA's request, the manufacturer of the new chickenpox vaccine, licensed by FDA March 17, 1995, will monitor several thousand vaccinated children for 15 years to determine the long-term effects of the vaccine and possible need for a booster immunization. (See "First Vaccine Available for Chickenpox" in the September 1995 FDA Consumer.)

For most vaccines, the government relies on the Vaccine Adverse Event Reporting System (VAERS) to identify problems after marketing begins.

FDA and the national Centers for Disease Control and Prevention manage VAERS, a system the two agencies developed in response to the National Childhood Vaccine Injury Act of 1986. Anyone--physicians, vaccine manufacturers, patients, or the parents of a patient--can report to VAERS an adverse event that may be associated with any vaccine.

"What we're most interested in with VAERS is identifying any new problem, particularly serious problems, that might be so rare that it wasn't noticed or detected during the clinical trials," says Ellenberg.

However, many events that might be associated with vaccines go unreported.

"We don't have to have 100 percent reporting," says Donlon. Ellenberg agrees. Still, she adds, "We need enough reports to permit detection of rare events and to allow us to make reliable comparisons of reporting rates among vaccine lots. Our ability to do this improves if doctors make more reports and make them more timely."

Donlon points out that the report of an adverse event to VAERS is not documentation that a vaccine caused the event. He says doctors shouldn't make that judgment.

"Just report it," he says, "even if you've never seen it before. Maybe many others around the country are seeing the same thing."

For example, a mother recently called FDA because her child's hair had fallen out each time the child received a dose of the hepatitis B vaccine. The mother said she asked the pediatrician whether the vaccine could have caused the hair loss, but the pediatrician was sure that couldn't be the case. In fact, after the second dose of the vaccine and subsequent hair loss, the doctor was preparing to do a scalp biopsy to determine the cause.

A search of the VAERS database found 45 cases of hair loss after hepatitis B vaccination. Of those, 15 cases were like this one, in which hair loss happened after each of two doses of the vaccine.

"That's called 'positive rechallenge,'" says Ellenberg, "and it gives you a much stronger belief that the event was actually due to the product. Now, hair falling out is not a life-threatening event. But if people are aware it could happen, then they won't be imagining

the worst, and invasive, unnecessary tests may not have to be performed."

Besides identifying previously unknown adverse events, VAERS is an important tool for monitoring individual lots of vaccines. "We don't expect there to be problems with vaccine lots," says Ellenberg, "because the regulations are very stringent. But even though we don't expect to find anything, we look [at the reports to VAERS] every week, and if there really was a problem with a lot, we could move very rapidly to get that lot off the market.

"One of the first things we do if we see a lot that has an elevated number of adverse events is look at its "sister" lots, the other lots that came from the same larger bulk lot. If those lots also have high rates of adverse events, it would raise our level of suspicion that there might be a problem. If, however, the other lots had average or even low rates, we would feel that this is just more likely chance variation."

Another key factor to assess the significance of the number of adverse events is the size of the lot.

"A lot with hundreds of thousands of doses is going to be associated with more events than a lot with tens of thousands of doses," says Ellenberg.

VAERS is designed to detect signals or warnings that there might be a problem rather than to answer questions about what caused the adverse event, according to "Research Strategies for Assessing Adverse Events Associated with Vaccines," a 1994 report by the Institute of Medicine. These signals can lead to hypotheses about causality, which can then be tested by other methods, such as epidemiologic or laboratory studies.

Background Rates Cause Confusion

"The problem with any vaccine that's given to very young children is that there are a lot of background adverse events occurring in the first year of life," says Ellenberg.

A reaction thought to be due to a vaccine may actually have been from something else, such as an ear infection, explains Hardegree.

Children less than a year old are at greatest risk for high fevers, seizures, and sudden infant death syndrome (SIDS). These events are seen both in the presence and absence of vaccination. The SIDS death rate is approximately 1.3 per 1,000 live births during the first year of life, according to Ellenberg. During that same period, babies receive the DPT vaccine three times--at 2, 4 and 6 months.

"You don't have to be a mathematician to appreciate the fact that, by chance, SIDS will sometimes occur shortly after the vaccine was administered," says Ellenberg. "The calculations that we have been able to do suggest that the numbers of SIDS following

vaccination that have been reported to VAERS are not beyond what would be expected by chance. And there have been some well-conducted, focused studies that demonstrate that SIDS is not associated with DPT vaccination. But, on the basis of VAERS data alone, we don't have proof that vaccines are not contributing to these problems and we certainly don't have proof that they are contributing."

Adding to the confusion is the fact that DPT is only one of many infant vaccines. The recommended childhood immunization schedule (192K PDF file) includes vaccines for hepatitis B, haemophilus b, measles, mumps, rubella, and polio, all during the first 12 months.

At the other end of the age spectrum, deaths are also reported after administration of the influenza vaccine. "Often these vaccines are given to people in nursing homes," explains Ellenberg. Unfortunately, this population has a relatively high death rate anyway, so it's almost impossible to say whether a given death is associated with the vaccine, she says.

As inevitable as some of those deaths, as well as other adverse events, may be, FDA remains vigilant in its efforts to improve vaccine safety. The agency will continue to be aggressive, says Hardegree, in its efforts, along with manufacturers and other government agencies, to get safer vaccines on the market.

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Assessing Risks with Polio Vaccines

In 1955, the year the polio vaccine was licensed, an individual lot of that vaccine infected 60 people directly and 89 who came in contact with them because the manufacturer had failed to totally inactivate the virus. But, as awful as that was, parents of other children weren't deterred from having their children vaccinated.

"When a disease is rampant, the public will accept high-risk products," says Jerome A. Donlon, M.D., Ph.D., director of CBER's Office of Establishment Licensing and Product Surveillance.

There have been no reported cases of paralysis caused by naturally occurring polio virus in the United States since 1979. However, according to the national Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, about six to eight people get polio from the live vaccine each year.

Unlike the vaccine-associated cases in 1955, these modern cases are not caused by manufacturing failures. Instead, most of the cases are in people with previously undetected immune deficiencies.

The problem is that the virus, though weakened, is still active. The committee is developing a new polio vaccination policy that will include a greatly enhanced role for inactivated (killed) polio vaccine.
--I.B.S.

Developing New Pertussis Vaccines

Recent results of pertussis (whooping cough) vaccine clinical trials show that three experimental vaccines are highly effective in infants.

The trials were sponsored by the National Institute of Allergy and Infectious Disease, part of the National Institutes of Health, in Bethesda, Md., and conducted in Italy and Sweden. The results also showed that the experimental vaccines caused fewer side effects than a vaccine currently used in the United States.

Scientists in FDA's Center for Biologics Evaluation and Research have been instrumental in developing and evaluating acellular vaccines, such as those tested in Italy and Sweden, and have collaborated with NIAID and the vaccine manufacturers to design the European trials.

Acellular vaccines contain only the parts of the pertussis bacterium thought to be important for immunity. U.S. vaccines licensed for use in infants are called whole-cell vaccines, because they contain the whole, inactivated pertussis organism.

Seizures were reported rarely in the trials, but no more frequently in any of the pertussis vaccine groups than in the control group. Side effects, such as redness, pain and swelling at the site of the injection, fever, and protracted crying, were reported less commonly with the acellular vaccines than with the whole-cell one.

FDA has made special efforts to encourage manufacturers to submit applications for the use of acellular pertussis vaccines in infants. The agency will target such applications for complete review within six months of receiving them. However, actual times to any licensing can vary, depending on the quality and completeness of the data submitted.

FDA recommends that parents continue to have their children vaccinated against pertussis with available vaccines.

All vaccines pose some risks of side effects, but for both whole-cell and acellular pertussis vaccines, serious, long-lasting problems are extremely rare. Pertussis itself can be fatal. (For more information, see "New Pertussis Vaccine Offers Prevention Alternative" in the September 1992 FDA Consumer.)
--I.B.S.

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